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WHAT IS CLAIMED \IS:

- 1. An solated nucleic acid encoding a polypeptide comprising at least one of the biological activities of OPG wherein the nucleic acid is selected from the group consisting of:
- a) the nucleic acids shown in Figures

 10 2B-2C (SEQ ID NO:120), 9A-9B (SEQ ID NO:122), and 9C-9D

 (SEQ ID NO:124) or complementary strands thereof;
 - b) nucleic acids which hybridize under stringent conditions with the polypeptide-encoding regions as shown in Figures 2B-2C (SEQ ID NO:120), 9A-9B (SEQ ID NO:122) and 9C-9D (SEQ ID NO:124);
 - c) nucleic acids which hybridize under stringent conditions with nucleotides 148 through 337 inclusive as shown in Figure 1A; and
 - d) nucleic acid which are degenerate to the nucleic acids of (a), (b) and (c).
 - 2. The nucleic acid of Claim 1 which is cDNA, genomic DNA, synthetic DNA or RNA.
- 3. A polypeptide encoded by the nucleic acid of Claim 1.
 - 4. The nucleic acid of Claim 1 including one or more codons preferred for Escherichia coli expression.
 - 5. The nucleic acid of Claim 1 having a detectable label attached thereto.
- 35 6. The nucleic acid of Claim 1 comprising the polypeptide-encoding region of Figure 2B-2C (SEQ ID

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NO:120), Figure 9A 9B (SEQ ID NO:122) or Figure 9C-9D (SEQ ID NO:124).

- 7. The nucleic acid of Claim 6 having the sequence as shown in Figure 9C-D (SEQ ID NO:124) from nucleotides 158-1297.
 - 8. An expression vector comprising the nucleic acid of Claim 1.
 - 9. The expression vector of Claim 8 wherein the nucleic acid comprises the polypeptide encoding region as shown in Figure 9C-9D (SEQ ID NO:124).
- 10. A host dell transformed or transfected with the expression vector of Claim 8.
 - 11. The host cell of Claim 10 which is a eucaryotic cell.
 - 12. The host cell of Claim 11 which is selected from the group consisting of CHO, COS, 293, 3T3, CV-1 and BHK cells.
- 25 13. The host cell of Claim 10 which is a procaryotic cell.
 - 14. The host cell of Claim 13 which is Escherichia coli.
 - 15. A transgenic mammal comprising the expression vector of Claim 8.
- 16. The transgenic mammal of Claim 15 which 35 is a rodent.

- 17. The transgenic mammal of Claim 16 which is a mouse.
- 18. A process for the production of OPG
- 5 comprising:

growing under suitable nutrient conditions host cells transformed or transfected with the nucleic acid of Claim 1; and

isolating the polypeptide products of the expression of the nucleic acids.

- 19. A purified and isolated polypeptide comprising OPG.
- 15 20. The polypeptide of Claim 19 which is mammalian OPG.
 - 21. The polypeptide of Claim 20 which is human OPG.
- 22. The polypeptide of Claim 19 which is substantially free of other human proteins.
- 23. The polypeptide of Claim 21 having the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123), or Figure 9C-9D (SEQ ID NO:125) or a derivative thereof.
- 24. The polypeptide of Claim 23 having the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 22-401 inclusive.
- 25. The polypeptide of Claim 23 having the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 32-401 inclusive.

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- 26. The polypeptide of Claim 19 which is characterized by being a product of expression of an exogenous DNA sequence.
- 5 27. The polypeptide of Claim 26 wherein the DNA is cDNA, genomic DNA or synthetic DNA.
 - 28. The polypeptide of Claim 19 which has been modified with a water-soluble polymer.
 - 29. The polypeptide of Claim 28 wherein the water soluble polymer is polyethylene glycol.
 - 30. A polypeptide comprising:
- an amino acid sequence of at least about 164 amino acids comprising four cysteine-rich domains characteristic of the cysteine rich domains of tumor necrosis factor receptor extracellular regions; and an activity of increasing bone density.
 - 31. A polypeptide comprising the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123) or Figure 9C-9D (SEQ ID NO:125) having an amino terminus at residue 22, and wherein from 1 to 216 amino acids are deleted from the carboxy terminus.
 - 32. The polypeptide of Claim 31 comprising the amino acid sequence from residues 22-185, 22-189, 22-194, or 22-201 inclusive.
 - 33. The polypeptide of Claim 32 further comprising an Fc region of human IgG1 extending from the carboxy terminus.

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- 34. A polypeptide comprising the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123) or Figure 9C-9D (SEQ ID NO:125) having an amino terminus at residue 22, wherein from 1 to 10 amino acids are deleted from the amino terminus and, optionally, from 1 to 216 amino acids are deleted from the carboxy terminus.
- 35. The polypeptide of Claim 34 comprising the amino acid sequence from residues 27-185, 27-189, 27-194, 27-401, or 32-401 inclusive.
- 36. The polypeptide of Claim 35 further comprising an Fc region of human IgG1 extending from the carboxy terminus.
 - 37. A polypeptide selected from the group consisting of:

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huOPG [22-201]-Fc
               huOPG [22-401]-Fc
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               huOPG [22-180]-Fc
               huOPG met [22-401]-Fc
               huOPG Fc-met [22-401]
               huOPG met [22-185]
               huOPG met [22 189]
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               huOPG met [22-194]
               huOPG met [27+185]
               huOPG met [[27 1/189]]
               huOPG met [27-1294]
               huOPG met [32-401]
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                huOPG met-ĭys[22-401]
                huOPG met [22-401]
                huOPG met [22-4\cdot 1]-Fc (P25A)
                huOPG met [22-40] (P25A)
                huOPG met [22-40] (P26A)
35
                                    (P26D)
                huOPG met [22-401]
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[22-194] (P25A) huOPG met huOPG met [22-194] (P26A) huOPG met met-(lys)3 [22-401] huOPG met met-arg-gly-ser-(his)6 [22-401]

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- A nudleic acid encoding the polypeptide 38. of Claim 37.
- An antibody or fragment thereof which specifically binds to OPG. 10
 - The antibody of Claim 39 which is a monoclonal antibody.
- A metho \d for detecting the presence of 41. 15 OPG in a biological sample comprising:

incubating the sample with the antibody of Claim 39 under conditions that allow binding of the antibody to OPG; and

detecting the bound antibody.

A method to assess the ability of a 42. candidate substance to bind to OPG comprising: incubating OPG/with the candidate substance

under conditions that allow binding; and 25

- measuring the bound substance.
- A method of regulating the levels of OPG 43. in an animal comprising modifying the animal with a nucleic acid encoding OPG! 30
 - The method of Claim 43 wherein the nucleic acid promotes an increase in the tissue level of OPG.

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- 46. A pharmaceutical composition comprising
 5 a therapeutically effective amount of OPG in a
 pharmaceutically acceptable carrier, adjuvant,
 solubilizer, stabilizer and/or anti-oxidant.
- 47. The composition of Claim 46 wherein the 10 OPG is human OPG.
 - 48. The composition of Claim 47 wherein the OPG has the amino acid sequence as shown in Figure 9B.
- 15 49. A method of treating a bone disorder comprising administering a therapeutically effective amount of the polypeptide of Claim 19.
- 50. The method of Claim 49 wherein the polypeptide is human OPG.

- 51. The method of Claim 49 wherein the bone disorder is excessive bone loss.
- 52. The method of Claim 51 wherein the bone disorder is selected from the group consisting of osteoporosis, Paget's disease of bone, hypercalcemia, hyperparathyroidism, steroid-induced osteopenia, bone loss due to rheumatoid arthritis, bone loss due to osteomyelitis, osteolytic metastasis, and periodontal bone loss.
- 53. The method of Claim 49 further comprising administering a therapeutically effective amount of a substances selected from the group consisting of bone morphogenic proteins BMP-1 through

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BMP-12, TGF- β family members, IL-1 inhibitors, TNF α inhibitors, parathyroid hormone and analogs thereof, parathyroid hormone related protein and analogs thereof, E series prostaglandins, bisphosphonates, and bone-enhancing minerals.

- 54. An osteoprotegerin multimer consisting of osteoprotegerin monomers.
- 10 55. The multimer of Claim 54 which is a dimer.
 - 56. The multimer of Claim 54 formed by interchain disulfide bonds.
 - 57. The multimer of Claim 54 formed by association Fc regions derived from human IgG1.
- 58. The multimer of Claim 54 which is 20 essentially free of osteoprotegerin monomers and inactive multimers.
- 59. The multimer of Claim 54 wherein the monomers comprise the amino acid sequence as shown in 25 Figure 9C-9D (SEQ ID NO:125) from residues 22-401, or a derivative thereof.
- 60. The multimer of Claim 54 wherein the monomers comprise the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 22-194.

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